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A Randomized Trial of Controlled-Release Oxycodone During Inpatient Rehabilitation Following Unilateral Total Knee Arthroplasty

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Background: Reliance on "as-needed" analgesia following total knee arthroplasty may lead to inadequate control of pain and delayed recovery of function. Preemptive use of controlled-release opioids may improve pain control, accelerate recovery, and reduce the need for inpatient rehabilitative services. This study was designed to determine whether controlled-release opioids enhance post-arthroplasty pain control and facilitate functional recovery during rehabilitation.

Methods: Fifty-nine patients admitted for inpatient rehabilitation following unilateral total knee arthroplasty were randomized to receive OxyContin (controlled-release oxycodone) (twenty-nine patients) or a placebo (thirty patients) every twelve hours. Both groups could receive on-request, immediate-release oxycodone (5 mg every four hours). The dose of study medication was increased on the basis of the frequency of requests for immediate-release oxycodone. Measures of interest included pain ratings as determined with a visual-analog scale, changes in the range of motion of the knee and quadriceps strength, and improvements in selected Functional Independence Measure scores during the first eight physical therapy sessions. The duration of the hospital stay for rehabilitation also was compared between the two groups.

Results: Baseline demographic, clinical, and functional characteristics were similar between the OxyContin and placebo groups. Compared with the placebo group, the patients who received OxyContin reported significantly less pain as well as significantly greater range of motion of the knee (passive motion, $p = 0.036$; active motion, $p < 0.001$) and quadriceps strength ($p = 0.001$) by the eighth physical therapy session. The patients who received OxyContin also were discharged from the rehabilitation hospital at an average of 2.3 days earlier than the patients in the placebo group ($p = 0.013$).

Conclusions: Preemptive use of controlled-release oxycodone during rehabilitation following total knee arthroplasty leads to improved pain control, more rapid functional recovery, and a reduced need for inpatient rehabilitative services.

Patients who undergo total knee arthroplasty often experience intense postoperative pain, particularly during efforts to mobilize and strengthen the affected extremity[1]. A reduction in postoperative pain after total knee arthroplasty is associated with an increase in the range of motion of the knee, faster mobilization, and a shorter hospital stay[2,3]. The intensity of pain following total knee arthroplasty is predictive of extended stays in rehabilitation hospitals[4] and aberrant gait patterns[5,6]. Pain intensity and residual functional limitations are closely related to patients' perceptions of success[7,8].

Although uncontrolled pain is an acknowledged impediment to postoperative functional recovery[9], strategies to ensure patient comfort during rehabilitation have yet to be extensively integrated into clinical practice. Typically, immediate-release opioids are prescribed on an as-needed basis to control pain following total knee arthroplasty. Often, a combined opioid-acetaminophen or opioid-aspirin formulation is administered every four to six hours on patient request. There have been well-documented problems with this approach consequent to both patient and caretaker-related barriers (for example, misinformation regarding addiction risk, patients' reluctance to trouble their caretakers, and delays in delivery of the analgesic after it has been requested)[10]. Given the expanding numbers of arthroplasties being performed, the optimal postoperative management becomes increasingly important as a medico-economic and public-health concern. If the adequacy of pain

control affects recovery of joint strength and range of motion, restoration of functional autonomy, and/or postoperative utilization of resources, the clinical and economic consequences of pain control could be substantial.

Controlled-release opioid preparations provide a reliable means of maintaining stable serum concentrations and avoiding the erratic fluctuations that may characterize immediate-release formulations; they also free patients from the onus of requesting as-needed pain medication. We conducted a randomized, double-blind, placebo-controlled trial to assess whether controlled-release opioids provide superior control of postoperative pain, result in better functional recovery, and reduce the duration of rehabilitation following unilateral total knee arthroplasty in comparison with on-request, immediate-release opioids.

Methods

The study was conducted at two affiliated freestanding acute-rehabilitation facilities and was approved by a central institutional review board.

All subjects screened for study participation had been transferred to a rehabilitation hospital within seven days following elective unilateral total knee arthroplasty performed for the treatment of osteoarthritis or rheumatoid arthritis. Patients were recruited between February 1, 1997, and September 30, 1997. Eligible subjects had to speak English, have rated their pain as moderate to very severe on a 5-point Likert-type scale (1 = none, 2 = mild, 3 = moderate, 4 = severe, and 5 = very severe), have been cleared to bear weight fully on the involved extremity at the time of admission to the rehabilitation hospital, have no history of substance abuse as assessed through administration of the Drug Abuse Screening Test[11], and have no evidence of cognitive impairment (a score of >27 as determined with the Mini-Mental State examination described by Folstein et al.[12]). There were no exclusion criteria based on age, functional status before the total knee arthroplasty, or pain severity or duration before the arthroplasty.

A total of 135 patients were screened, and fifty-nine (44%) were enrolled in the study. Reasons for nonenrollment included transfer back to an acute-care institution due to medical instability (2%) and the patient's refusal to participate (54%). Enrolled and nonenrolled subjects were similar with respect to race ($p = 0.99$), sex ($p = 0.51$), and age ($p = 0.44$). The median pain rating of the patients who were enrolled in the study was 0.6 point higher than that of the patients who were not ($p = 0.05$).

Study subjects were approached on the day of admission to the rehabilitation hospital and were screened for eligibility. After subjects had provided written informed consent they were randomized at a central pharmacy in blocks of ten. Patients were randomized separately for the two participating facilities, since the site of the rehabilitation-service delivery was believed to be a potential confounder.

In the intervention group, patients received opaque white capsules containing 10 mg of OxyContin (oxycodone) at 8:00 PM and opaque blue capsules containing 20 mg of Oxy-

TABLE I Comparison of Selected Outcomes of Patients Treated with OxyContin with Those Treated with a Placebo

Measure	Placebo (N = 29*)	OxyContin (N = 29)	P Value
Visual-analog pain scores at therapy-day 8†			
At end of physical therapy	5.9 ± 1.5	4.8 ± 1.7	0.012
Worst during physical therapy	7.4 ± 1.5	6.6 ± 1.9	0.060
Degree to which pain interfered with physical therapy	6.3 ± 1.6	5.4 ± 1.8	0.033
Change in functional measures from therapy-day 1 to therapy-day 8†			
Passive knee range of motion *(deg)*	24.8 ± 10.2	30.7 ± 10.6	0.036
Active knee range of motion *(deg)*	19.9 ± 9.6	30.4 ± 9.9	<0.001
Knee extension torque *(lb†)*	8.8 ± 4.0	13.7 ± 6.2	0.001
Functional Independence Measure score[15]† *(points)*			
Transfers	1.6 ± 0.8	2.0 ± 0.7	0.069
Walking	2.3 ± 0.8	2.8 ± 1.2	0.056
Immediate-release climb	2.4 ± 0.9	3.2 ± 1.4	0.011
Distance walked *(ft§/3 min)*	99.5 ± 49.4	132.8 ± 48.5	0.014
Length of stay† *(days)*	15.3 ± 3.2	13.0 ± 3.7	0.013
Discharge plan *(no. [%] of patients)*			
No physical therapy	0 (0)	1 (3)	0.501
Outpatient physical therapy	15 (52)	18 (62)	
Home physical therapy	11 (38)	9 (31)	
Transfer to subacute rehabilitation facility	3 (10)	1 (3)	

*One patient was lost to follow-up due to emergency admission to an acute-care hospital. †The values are given as the average and the standard deviation. †1 lb = 1.358 N. §1 ft = 0.3048 m.

Contin at 8:00 AM. Patients assigned to the control group received identical capsules containing lactose on the same dosing schedule. Both groups had standing orders for immediate-release oxycodone, 5 mg every four hours, as needed. The study therapy was initiated on the evening following admission to the rehabilitation hospital.

The starting dose of OxyContin (20 mg in the morning and 10 mg in the evening) was arbitrary and deemed unlikely to be optimal for all patients in the OxyContin group. Therefore, a blinded upward titration of the OxyContin regimen based on the number of times that the patient received on-request, immediate-release oxycodone was adopted. Patients who received three or more on-request 5-mg doses of immediate-release oxycodone on two consecutive days had the OxyContin dose increased by 10 mg. They then received 20 mg of OxyContin in the morning and 20 mg in the evening contained in opaque blue capsules. The upward titration was continued to a possible maximum OxyContin dose of 30 mg in the morning and 30 mg in the evening. Patients in the placebo group underwent a similar titration of study medication contingent on their utilization of rescue doses; however, they continued to receive opaque capsules containing only lactose.

Patients in both groups also had standing orders for a bowel regimen (docusate sodium, 100 mg, and senna three times a day; lactulose, 20 g three times a day on request; and a Fleet enema once a day on request), acetaminophen (325 to 650 mg every six hours on request), and an antiemetic medication (Torecan [thiethylperazine], 10 mg every eight hours on request). All patients used a continuous-passive-motion machine for two and one-half hours each evening at a starting range of 80° to 100° of knee flexion, which was increased as tolerated.

Both groups participated in a standard, rigorous rehabilitation program for three hours each day. The program consisted of range-of-motion activities, progressive resistive exercises, and instruction in transfers, walking, and negotiation of stairs and uneven surfaces. All subjects had physical therapy orders for the use of topical thermal modalities (ice packs and hydrocollators) and/or electrical stimulation to be used on an on-request basis for the alleviation of pain associated with the total knee replacement.

Data were collected at various time-points throughout each subject's stay in the rehabilitation hospital. At baseline, information was collected regarding sociodemographic characteristics, the visual-analog pain scores before and after the total knee arthroplasty, the degree of arthritis in other joints, and the duration of pain prior to the total knee arthroplasty.

During the follow-up period, visual-analog pain scores were recorded immediately following each full weekday physical therapy session. Subjects were requested to rate their pain "right now" and "at worst during physical therapy." They also were asked to rate the degree to which the pain interfered with their ability to participate in physical therapy. The validity of this type of interference score has been demonstrated through use of the Brief Pain Inventory[13,14].

Initial and final panels of physical performance variables were collected at the first and eighth weekday physical therapy sessions by the treating physical therapist. The active and passive ranges of knee motion, quadriceps strength, distance that the patient could walk safely in a three-minute interval, and selected Functional Independence Measure scores[15] were determined by therapists to assess the patients' functional status, establish appropriate therapeutic goals, and gauge the rate of recovery. The passive and active ranges of motion were determined, with use of a standard goniometer, with the subjects in a sitting-supported position to normalize the degree of hip flexion. Three values for both the passive and the active range of motion were recorded, and the highest value was used in the data analysis. Knee extensor, or quadriceps, strength was measured in pounds with use of a Chatillon CSD400C handheld dynamometer (Chatillon, Greensboro, North Carolina)[16,17].

Functional Independence Measure scores for walking, sit-to-stand transfers, and stair-climbing were included in the panel of variables collected during the first and eighth weekday physical therapy sessions. The treating physical therapists assigned Functional Independence Measure scores to the patients on the basis of their observed performance during therapy. The subjects' speed of walking was determined by recording the distance safely traversed during a three-minute period. A carefully measured rectangular course circumscribing the physical therapy gym was used for this purpose.

The Memorial Symptom Assessment Scale[18] was administered to the subjects following the sixth physical therapy session. A subscale of the Memorial Symptom Assessment Scale was found through factor analysis to be sensitive for detecting the presence and severity of opioid-related side effects. Although the full Memorial Symptom Assessment Scale instrument was administered, values for this subscale were used during data analysis to determine whether the OxyContin and control groups differed in the degree to which they experienced and were distressed by opioid-induced side effects.

Length of stay was recorded at the time of discharge from the rehabilitation hospital, as was the plan for any additional physical therapy. Possible disposition plans consisted of transfer to a subacute-rehabilitation facility, enrollment in home or outpatient physical therapy, or no additional physical therapy.

Selected patient characteristics, preoperative and postoperative visual-analog pain scores, and functional measures on the first day of physical therapy were compared between the OxyContin and placebo groups. Outcome measures that were compared included visual-analog pain scores (at the end of physical therapy, the worst during physical therapy, and the degree to which pain interfered with physical therapy) and change in functional measures; the latter was calculated by subtracting scores recorded at the first physical therapy session from those recorded at the eighth. Length of stay in the hospital and discharge plans were also compared. P values were calculated with use of a two-tailed t test for continuous measures and a chi-square test for dichotomous measures; a nominal value of $p < 0.05$ was used to establish significance.

Results

The average age of the fifty-nine study subjects was sixty-five years (range, forty-six to eighty-five years); twenty-

nine (49%) were male. The OxyContin and placebo groups were similar with respect to demographic and clinical characteristics. Visual-analog pain scores were consistently high in both groups during both the preoperative and the postoperative period (average, 7.8 for both periods), and neither the pain scores nor the functional measures at the first physical therapy session differed between the two groups. Of the fifty-nine patients enrolled in the study, twenty-nine were randomized to receive OxyContin and thirty, to receive a placebo.

Seven patients (three in the OxyContin group and four in the placebo group) discontinued taking the study medication; they continued to be followed, however, for the outcomes of interest and were included in all analyses. The three patients in the OxyContin group expressed a desire to have greater control over their immediate-release medication, whereas the four patients in the placebo group gave inadequate analgesia as the reason for discontinuing the study medication. Outcome data were unavailable for one patient in the placebo group; that patient was lost to follow-up because of emergency admission to an acute-care hospital.

The patients in the OxyContin group requested an average of 1.9 doses of rescue medication per day—that is, immediate-release oxycodone (5 mg per dose) to control pain that was inadequately managed by the study medication—whereas those in the placebo group requested an average of 2.6 doses per day ($p = 0.02$). As a consequence, the dose was titrated to the highest dose of study medication for only 7% (two) of the twenty-nine patients in the OxyContin group compared with 43% (thirteen) of the thirty in the placebo group. Total daily consumption of oxycodone (controlled-release plus immediate-release) by the patients randomized to OxyContin therapy was more than four times higher than that by the patients in the placebo group (54.4 and 12.9 mg, respectively; $p < 0.001$). Comparison of the scores on the Memorial Symptom Assessment Scale on the sixth day of the study, however, revealed no difference between the two groups with regard to opioid-related side effects; the scores averaged 3.8 and 3.9 in the OxyContin and placebo groups, respectively ($p = 0.830$).

The pain scores at the eighth physical therapy session were uniformly lower for the patients in the OxyContin group (Table I). With the numbers available, no significant differences were detected between the OxyContin and placebo groups with regard to physiologic or functional measures at the first physical therapy session. The patients treated with OxyContin had greater improvement than the placebo group in all functional measures; the difference between groups approached or achieved significance for all seven measures.

The patients in the OxyContin group were discharged from the rehabilitation hospital at an average of 2.3 days earlier than those in the placebo group (13.0 compared with 15.3 days; $p = 0.013$). The duration of the acute hospitalization was not factored into the determination of the length of stay in the rehabilitation hospital. The patients who received the placebo were nominally more likely to be discharged to home physical therapy or transferred to a subacute-rehabilitation facility.

Discussion

Our findings indicate that patients who receive preemptive treatment experience less pain, recover knee strength at an accelerated rate, and utilize fewer health-care resources. The patients in the OxyContin group received controlled-release opioid in addition to rescue doses of immediate-release opioid; they also received a higher total average daily dose of opioid than did the patients in the placebo group. The extent to which these differences contributed to the study results is less important than the fact that the preemptive approach to pain management involved rapid titration to meet each patient's opioid requirement. This analgesic strategy differs markedly from the current practice of using as-needed opioid or nonsteroidal anti-inflammatory drugs for pain management, which can result in unrelieved pain and delayed functional recovery[8].

The intervention strategy employed in this study—using rescue doses to relieve pain that was inadequately relieved by a controlled-release opioid preparation and to guide its upward titration—is supported by extensive clinical experience in the management of cancer-related and postoperative pain. Nonsteroidal anti-inflammatory drugs and adjuvant analgesics may be used as valuable supplements to opioid analgesia. In our experience, however, the use of nonsteroidal anti-inflammatory drugs or adjuvants in isolation rarely controls pain adequately during aggressive mobilization after total knee arthroplasty.

One of the most important benefits afforded by controlled-release opioid preparations is the maintenance of relatively constant serum opioid levels. The constant analgesia provided by stable serum oxycodone levels may have facilitated the intervention group's recovery in a variety of ways. Formal therapy sessions lasted only a total of three hours per day; enhanced ongoing pain control may have allowed the patients in the intervention group to remain active outside of formal physical therapy sessions. Enhanced baseline analgesia also may have diminished central sensitization, the permissive effect of nociceptive impulses on the central nervous system's response to additional noxious stimuli[19]. Better constant analgesia may have reduced the development of aberrant biomechanical patterns[20] in the intervention group and may have facilitated the recovery of normal movement. Finally, a growing body of literature supports the role of peripheral opioid receptors in mediating local inflammatory responses[21,22]. The exuberant soft-tissue inflammation that typically develops following total knee arthroplasty may have been attenuated by stable serum opioid levels. The degree to which these potential benefits were conferred by the use of controlled-release oxycodone must remain speculative.

Our sample was derived from a population referred for acute inpatient rehabilitation after total knee arthroplasty; this distinguishes this series from the growing number of patients who are discharged directly to home following arthroplasty. Many of our patients reported severe pain at the arthroplasty

site and likely fall within a subset of patients experiencing greater pain after total knee arthroplasty. Patients who consented to participate in the study had higher pain scores than those who did not consent, suggesting that our study attracted patients for whom pain was a substantial problem. It is unclear if our findings are generalizable to a population of patients less troubled by pain.

Despite these limitations, we believe that our study has important clinical and economic implications. As financial pressures build to limit the use of rehabilitative services following total knee arthroplasty, timely recovery of function with effective control of symptoms becomes increasingly important. Our results indicate that preemptive pain control with a controlled-release opioid appropriately titrated to each patient's needs during rehabilitation accelerates functional recovery and reduces the utilization of health-care resources. ■

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